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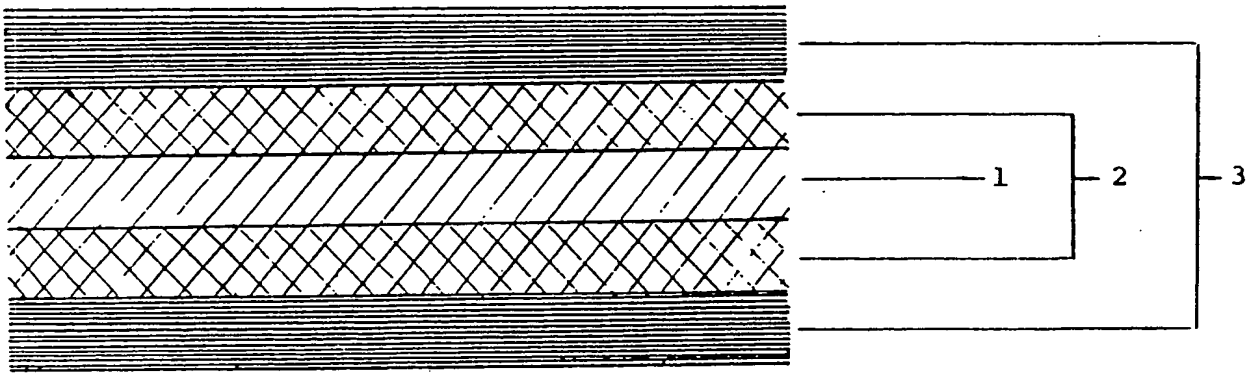


(57) Abstract

The present invention contemplates an implant device capable of releasing an active ingredient in an animal following administration thereto, said implant device comprising as an active ingredient at least one type of bioactive molecule, optionally admixed with one or more pharmaceutically acceptable carriers and/or excipients, substantially contained within a core matrix of a body member, said body member further comprising a membrane forming a wall around all or part of the core matrix and comprising material which is substantially impervious to the active ingredient and having at least one portion through which the active ingredient is capable of being relesead either directly or after a period of time in a continuous or pulsatile manner.

IMPROVED IMPLANTS

The present invention relates generally to an implant device for the administration of one or more bioactive molecules to animals including humans. The device may be adapted for continuous release or pulsatile release of the bioactive molecules.

An ideal delivery device administers bioactive agents to a target at a level which achieves the desired therapeutic effect. For bioactive molecules with short *in vivo* half-lives (such as some hormones and proteins), it is often desirable for the device to deliver at a constant release rate (i.e. zero order kinetics). For this purpose, a membrane-reservoir device may be used. A membrane reservoir device consists of a core of the biologically active material surrounded by a release-rate limiting membrane.

For the release to proceed at a constant rate, it is necessary to maintain the drug reservoir at a saturated level for the scheduled period of treatment. With the membrane delivery device, whilst the duration of the constant drug release is dependent on the size of the drug reservoir, the rate at which the drug is released is determined by the geometry of the device and the physico-chemical nature, thickness and surface area of the release-rate limiting membrane (1,2).

In spite of the desirability of a constant drug release rate, membrane reservoir devices are not used extensively because of technical difficulties associated with their fabrication in mass production (4). A more serious disadvantage of membrane reservoir devices is the fact that the core active material can be released by dumping whenever the release-rate limiting membrane is ruptured. This is highly undesirable in therapeutic treatment.

Common types of low cost and easily manufactured delivery devices are tablets or granules which use the dissolution-diffusion release mechanism (5). In these delivery devices, the active material is uniformly incorporated, by dissolution or dispersion in a matrix material (4). However, with these types of delivery devices, the release of the incorporated active materials displays a time-dependent continuously decreasing rate (i.e. a first order kinetics) (6). This phenomenon is believed to be the consequence of the progressively increasing diffusion resistance and decreasing area at the advancing diffusion front as diffusion proceeds from the matrix periphery inwards (6). In an attempt to modify the inherently first order release characteristics of drug dissolution and diffusion from a matrix material, the geometric shape of the delivery device has been modified to compensate for the increasing diffusion distance and decreasing area of the advancing diffusion front. For example, a hemispherical polymer matrix which is coated on all surfaces with an impermeable coating except for an aperture in the flat centre face has been shown to provide a near constant rate of drug release (8). Another example consists of a cylinder with impermeable wall coating and a longitudinal slit opening inward to a concave circular sector cross section. The release rate from this elegant device also showed a substantially uniform rate (9). In these geometric forms, the increase in diffusional distance and consequently the decrease in diffusion rate have been compensated by the increase in the surface area at the advancing diffusion front.

Although the most important attribute of a controlled release drug delivery device is its capability to maintain a therapeutically effective level of drug in the animal body over a scheduled period of time, its adoption ultimately depends on the cost, convenience, and ease of its fabrication and administration (10).

In terms of the ease and convenience of administering these devices as implants, shapes like sheets, films, microcapsules or hemispheres are generally impractical. Only rods, needles or cylinders are readily adapted for parenteral implantation using a conventional hypodermic needle.

A need accordingly exists for a simple and economical manufacturing process for implants which can release bioactive materials and which can be readily adapted for immediate continuous release or immediate or delayed pulsatile release of these molecules.

Accordingly, one aspect of the present invention contemplates an implant device capable of releasing an active ingredient in an animal following administration thereto, said implant device comprising as active ingredient at least one type of bioactive molecule, optionally admixed with one or more pharmaceutically acceptable carriers and/or excipients, substantially contained within a core matrix of a body member, said body member further comprising a membrane forming a wall around all or part of the core matrix and comprising material which is substantially impervious to the active ingredient and said body member further having at least one portion through which the active ingredient is capable of being released either directly or after a period of time in a continuous or pulsatile manner.

The intended recipient of the implant device is preferably a human, livestock animal including a ruminant animal (e.g. a sheep, cow, horse, pig, goat or donkey), poultry (e.g. chicken, turkey, goose or game bird), a laboratory test animal (e.g. a rabbit, guinea pig or mouse), companion animal (e.g. dog or cat) or a wild animal in the captive or free state.

The bioactive molecule in the active ingredient comprises any native, synthetic or recombinant pharmaceutical agent or food additive or supplement including antigens, antibodies, cytokines, growth promotants, hormones, cancer cell inhibitory molecules or agents, immune stimulants or suppressants, anti-microbial agents including antibiotics, anti-viral agents, vitamins, minerals or inorganic or organic nutrients. The active ingredient may comprise one type of bioactive molecule or may be a mixture of different bioactive molecules.

Administration of the implant device may be by any convenient means but is generally by oral ingestion or injection *via* the intravenous, intraperitoneal, intramuscular, sub-cutaneous or intradermal route. The device may also be surgically implanted or implanted by sub-surgical procedures such as during biopsy procedures.

The pharmaceutical carriers and excipients include any and all dispersion media, coatings, antibacterial, anti-fungal and/or antiviral agents and the like as well as salts such as dicalcium phosphate. Additional components which may be included are binders (e.g. gum gragacanth, acacia, corn starch or gelatin), disintegrating agent (e.g. corn starch, potato starch, alginic acid and the like) and/or a lubricant (e.g. magnesium stearate). All such components, carriers and excipients must be substantially pharmaceutically pure and non-toxic in the amounts employed and must be biocompatible with the bioactive molecules.

The amount of bioactive molecule used in a given implant will vary depending on the type of bioactive molecule, condition in the animal being treated and the presence or absence of agonists to the bioactive molecule or antagonists to the condition being treated. In general, an effective amount of bioactive material is employed meaning an amount effective to induce, stimulate, promote or otherwise initiate the immediately intended result. For example, if the bioactive molecule is an antigen, the effective amount is that required to stimulate an immune response to the antigen. Commonly, the bioactive molecule will be present in amounts ranging from a few micrograms to gram quantities per implant device.

The body member of the implant device may be in any shape including elongate, oval, round, ball, hemispherical, capsule, rod, needle, cylinder, sheet, film or microcapsular shape. Conveniently, the shape is an elongate, cylindrical, rod or needle shape. In a most preferred embodiment, the implant device is elongate or generally cylindrical.

The walls encasing the body member are generally membranous or polymeric and are substantially impervious to the active ingredient and body fluid. It will be appreciated, however, that for practical purposes, some active material may be delivered through the walls of the body member but the majority of the active material will be delivered or released through a pre-determined region in the wall encasing the body member or as a result of rupture of the wall encasing the core body member again at a predetermined position in the case of delayed pulsatile release. The pre-determined region may be a pore, outlet, exit, channel or other passage formed within the body wall or may be a region defined during manufacture which is not covered by the wall. For example, in its most preferred embodiment, the body member is elongate, or more preferably generally cylindrical, having terminal portions capable of releasing the active ingredient contained within the core body member. Conveniently, during manufacture, the ends of the body member are open or sealed or partially sealed with a biodegradable polymer or other suitable material such that the end seals will degrade sufficiently to permit the active ingredient to be released.

In accordance with this preferred aspect of the invention there is provided an implant device capable of releasing an active ingredient in an animal following administration thereto, said implant comprising as an active ingredient at least one type of bioactive molecule, optionally admixed with one or more pharmaceutically acceptable carriers and/or excipients, substantially contained within a core matrix of an elongate body member, said body member further comprising a membrane forming a wall around all or part of the core matrix and comprising material which is substantially impervious to the active ingredient and said elongate body member having at least one terminal portion through which the active ingredient is capable of being released either directly or after a period of time in a continuous or pulsatile manner.

Preferably, the elongate body member possesses two terminal portions through which the active material is capable of being released. The active ingredient releasing end or ends of the body member may be open, partially sealed or completely sealed. Where the latter is the case, the end seals are materials capable of degrading or rupturing at some time after administration into the animal.

As used herein, where the body member contains a biodegradable seal (e.g. at a terminal portion of the body member), the period of time before this seal is degraded may range from a few minutes to a few hours or even a few days.

In a most preferred embodiment, the present invention contemplates an implant device capable of releasing an active ingredient in an animal following administration thereto, said implant comprising a generally cylindrical or elongate device containing at least one bioactive molecule, optionally admixed with one or more pharmaceutically acceptable carriers and/or excipients, wherein the device is adapted such that a substantial amount of the active material is able to be released via end portions of said device.

In yet another aspect of the present invention, the body member may comprise a plurality of alternating layers of active ingredient and walls substantially impervious to said active ingredient. In accordance with this embodiment, the implant device may contain only one type of bioactive molecule or may contain different types of bioactive material, released continuously or in a pulsatile manner. Again, the preferred body member is elongate and more preferably generally cylindrical in shape with terminal portions open, sealed or partially sealed as hereinbefore described. Conveniently, each layer may in turn be exposed to the animal's body fluids or all or most of the layers may be exposed simultaneously permitting, for example, the release of different active ingredients simultaneously or the same active ingredient in a pulsatile manner. The process for manufacture of the implant device according to this aspect of the invention is

conveniently achieved by a cyclical manufacturing process which is repeated until as many layers as required are formed.

According to this aspect of the present invention there is contemplated an implant device capable of releasing an active ingredient in an animal following administration thereto, said implant device comprising as an active ingredient at least one type of bioactive molecule, optionally admixed with one or more pharmaceutically acceptable carriers and/or excipients, substantially contained within a body member comprising a plurality of matrices interspaced by a plurality of layers of material substantially impervious to the active ingredient and said body member coated by a membrane comprising said material and said body member further comprising at least one portion through which the active ingredients in each layer are simultaneously or sequentially capable of being released either directly or over a period of time. Preferably, the body member is substantially elongate or generally cylindrical and the active ingredients are released through the terminal portions of the elongate or cylindrical body. Each layer may be exposed simultaneously or sequentially. The terminal portions may also be sealed completely or partially with a biodegradable material, which, for example, degrades in the presence of body fluids.

Still another aspect of the present invention provides a method of preparing an implant device comprising fabricating a body member containing an active ingredient, said body member having walls substantially impermeable to the active material and further having a region through which the active ingredient is capable of being released in a controlled manner either directly or after a period of time. Preferably, the active material is formed on a central support. Reference herein to the coating as being "substantially impermeable" is meant that in the time frame of delivery of active material from the device only a minor proportion is released *via* the coated walls relative to delivery via the ends of the device.

The resultant implant cast of the core body member may range in length from twenty millimetres to a metre long and can then be reduced to smaller segments of the desired length by cutting across the longitudinal axis of the implant. Alternatively, individual segments of desired size and shape may be pre-moulded.

It will be immediately apparent that there are alterantive ways of manufacturing the implant. For example, the core matrix may be cast, sectioned, coated and then separated. All such variations are encompassed by the present invention. Additionally, for manufacture of multiple layers of matrix interspaced with impervious membrane, the latter may form the core for the next matrix and so on.

The invention will be further described by reference to the following non-limiting figures and examples.

In the Figures:

Figure 1 is a schematic representation of the process of preparing implants according to the invention. The steps involved are casting 1, cast drying 2, coating 3 and cutting 4. A: Central support; B: Cylindrical cast containing active ingredient; C: Dry cast; D: Impermeable polymer coating; E: separated and cut implants.

Figure 2 illustrates the effect of changes in agar concentration in matrix on release profile.

Figure 3 shows the effect of implant length on the release of incorporated haemoglobin from open ended implants. A2, A4, A6, A8, A10 and A20 represent the release profiles from implants of 2, 4, 6, 8, 10 and 20 mm in length. The incorporating matrix contained 3% w/v agar. The plot points represent a summation of implants which have a constant summed length.

Figure 4 illustrates the effect of sealing one end of a cylindrical implant, 5 or 10 mm in length, with polymerised n-butyl cyanoacrylate, on the release of haemoglobin. The incorporating matrix contained 3% w/v agar.

Figure 5 is a schematic representation of a form of the implant device having multiple alternating layers of active ingredient interspaced with dividing walls of impervious material. A first implant 1 is prepared as in Figure 1 and the process is repeated to result in subsequent layers, e.g. 2, 3. The terminal portions of the multilayered implant device may be open to permit simultaneous contact of the active ingredient with body fluid or one or of the layers may be sealed with a biodegradable material.

Referring to Figure 1, a central support (e.g. a nylon string, polypropylene rod, or surgical suture) is positioned at the radial centre in a cylindrical mould using appropriate positioning guides. For water based polymeric matrices, the inner surface of the mould should be lined with material such as teflon to facilitate cast removal.

The mould (in a vertical orientation) is preferably pressure-filled from the bottom with an admixture of bioactive material, polymeric matrix, and excipient(s) according to the formulation used. After the cast is formed, the half-cylinder moulds are removed. The fresh cast may be then coated with polylactic acid (PLA)/polyglycolic acid (PLG) (85:15) co-polymer by dipping and air drying to form a water impermeable coating to thereby produce the body member. Alternatively, the dry cast may be coated with a water impermeable co-polymer such as n-butyl cyanoacrylate (3M-Vetbond ™).

The surface-coated cylindrical cast is then trimmed to segments of the desired length, usually 10 or 15mm, for use as implants.

The two cut ends of each segment individually moulded or sectioned prior to or subsequent to coating may be left open for the release of the bioactive material or one end may be sealed to form an implant releasing only from one end of the implant. When both ends are sealed, the device represents a package of the bioactive material which remains "dormant" for as long as the end cap is intact. This process may be repeated creating a plurality of layers interspersed with active ingredients (see Figure 5).

The effectiveness of n-butyl cyanoacrylate (3M-Vetbond™) in sealing the ends has been investigated. A 200 mm long cylindrical cast containing haemoglobin as a release indicator was incorporated in a gelatin agar matrix (5% w/v gelatin, 1% w/v agar) and formed on a centrally supported nylon string (diameter - 0.4mm). The cast was air dried at room temperature and then coated by five cycles of dipping and air drying with a solution of PLA/PLG (85:15) co-polymer (100 mg/ml in acetone). The dried cast was then cut into segments 10 mm long.

The cut ends of each segments were moisturised by contacting the surface of a drop of distilled water. After being in contact with the water for 3-5 minutes to wet the cut ends, the ends were blotted dry with sorbet paper towel and then coated by contacting body member with the surface of a drop of n-butyl cyanoacrylate on a clear white tile. One crop of n-butyl cyanoacrylate was used for the two cut ends of one segment. The treated segments were allowed to dry at room temperature for a period of 6 hours before testing *in vitro* or *in viva*.

When segments sealed with cyanoacrylate at both ends were incubated at 37 °C in water or phosphate buffer pH 7.0 containing 0.1% w/v sodium azide (5ml medium for one segment), no release of the incorporated haemoglobin was observed over a period of five weeks as determined by spectrophotometric measurements of the incubation medium. To ensure the ends of the device are sealed, it important to ensure the cut ends of the dry cast are properly moisturised before applying the n-butyl cyanoacrylate.

For segments with unsealed ends, the release of incorporated haemoglobin was found to be continuous for a period of over two weeks (Figure 2). About sixty per cent of the released haemoglobin was released in the first week of incubation. The release rate appeared to be time-dependent suggesting a diffusion dominated mechanism with the gelatin agar matrix material used in these trials. However, it is believed that release of bioactive from the device of the present invention is less time dependent (zero order) when other matrix material such as poly ortho esters or copolymers of collagen poly (HEMA) hydrogel are used as the incorporating matrices. These matrix materials have been shown to be bioerodible releasing incorporated 5-flurouracil in a zero order kinetic mode from a flat disc shaped structure (10).

For manipulating the release characteristics, the release mode of the present device can also be modified by the concentration and composition of the matrix materials. As shown in Figure 2, when the agar concentration in the matrix was lowered, the release was faster and the extent of release higher.

TABLE 1

Agar and gelatin contents in the matrix on haemoglobin release from open end segments (10 mm long)

% Gelatin (w/v)	0	5	10	0	5	10
	Day 1			Day 3		
0.7	1.281	1.406	1.302	2.365	2.625	2.576
1.0	1.056	1.268	1.165	2.007	2.419	2.241
2.0	0.992	1.246	1.179	1.786	2.338	2.308

% Gelatin (w/v)	0	5	10	0	5	10
	Day 5			Day 7		
0.7	2.705	2.928	2.853	2.836	3.123	3.013
1.0	2.490	2.817	2.657	2.772	3.067	2.869
2.0	2.271	2.810	2.742	2.575	3.107	2.985

(i) Data in Table 1 are absorbancies of haemoglobin released into solution on incubation of the open end segments at 37 °C.

(ii) Individual data are averages of four segments.

(iii) Haemoglobin loading per 10 mm segment: 9 mg.

TABLE 2

EFFECT OF MATRIX COMPOSITION ON THE RATE OF HAEMOGLOBIN RELEASE FROM CYLINDRICAL SEGMENTS (10 MM)

Matrix Composition 10% gelatin with agar at (w/v)	Cumulated haemoglobin release/day								
	Day of Release	1		3	5	7	9	11	15
	+	-	+	-	+	+	+	+	+
0.1%	0.376	1.286	0.248	0.434	0.186	0.139	0.105	0.083	0.050
0.2%	0.298	1.221	0.202	0.405	0.150	0.112	0.078	0.053	0.032
0.3%	0.369	1.341	0.247	0.444	0.181	0.138	0.108	0.085	0.058
0.4%	0.393	1.313	0.250	0.430	0.183	0.134	0.100	0.075	0.047
0.5%	0.343	1.212	0.225	0.399	0.165	0.119	0.085	0.063	0.042
0.6%	0.394	1.141	0.280	0.381	0.203	0.141	0.105	0.083	0.054
0.7%	0.321	1.053	0.229	0.347	0.167	0.117	0.088	0.069	0.048
0.8%	0.395	1.317	0.294	0.431	0.211	0.148	0.114	0.089	0.063
1.0%	0.333	1.186	0.228	0.391	0.191	0.137	0.105	0.083	0.055

(i) Data in Table are cumulated absorbancies of haemoglobin released per day into solution on incubation at 37°C of cylindrical segments. Segments coated with PLA/PLG co-polymer of their longitudinal cylindrical surface (i.e. open end segments) were designated as + and those entirely uncoated -.

In Table 1, the data show that gelatin agar composite matrices tend to release haemoglobin faster than agar-only matrices.

When gelatin-only matrices were used, the release was fastest as the gelatin matrices became solubilised at 37 °C upon hydration with water. Release of haemoglobin from gelatin-only matrices was completed within one day of incubation of 37 °C.

Modulation of the release of haemoglobin from gelatin based matrices can be effected by the inclusion of agar but the effect using the amounts of agar shown in Table 2 was complex bearing no apparent direct dependency on the agar concentrations.

Another parameter useful in modulating the release of haemoglobin from open end segments is the length of the device. Expressed as the equivalent total of released haemoglobin, the release from ten segments of 2 mm long was much faster than that from one segment of 20 mm long or two segments of 10 mm long (Figure 3). The rate and the extent of release over a two week period was markedly dependent on the length of the device. While short segments reached the maximal release extent at a faster rate within three or four days of incubation, longer segments appeared to release continuously over two weeks.

Consistent with a diffusion dominated mechanism of release of haemoglobin from the particular matrix material used in these trials, the inventors observed that the release rate was dependent on the initial amount of haemoglobin loaded, the rate being faster for higher loadings.

The implant device of the present invention may result in release of the active ingredient continuously over a period of time through the unsealed ends of the device. A delayed and/or pulsatile effect may be obtained by sealing the ends with a biodegradable material or by making a body member with multiple layers.

Parameters which can modify the release characteristics of the bioactive material including sealing the open ends of the cylindrical device with n-butyl cyanoacrylate (3M-Vetbond™). The release of haemoglobin from this device can be completely arrested when both ends were treated with cyanoacrylate. The release would be different when one rather than both ends of the cylindrical device was kept open (Figure 4).

Figure 4 shows a comparison of release of incorporated haemoglobin from segments which either have or have not ends sealed with n-butyl cyanoacrylate. The release rate of haemoglobin from segments with one end closed were slower but the duration of continuous release was substantially extended compared to those with both ends open. Apparently sealing one end of a segment slowed down the release making it look like coming out from an open end segment twice in length (refer to Figure 3) and at the same time made the release less time dependent. Hence, sealing one of the cut ends of segments provides a practical means of modulating the release characteristics of the delivery device. As described earlier, when both ends were sealed, release of the incorporated haemoglobin was completely prevented. However, if tiny holes were made by pricking through the end coating, even slower and longer lasting release of haemoglobin may be effected and this embodiment comes with the scope of the present invention as a substantial amount of the active is released from the ends of the implant device.

One major problem in the field of drug device development is the availability of simple and economical mass production method. The present invention provides such a method for fabricating a device which can release a comprehensive range of bioactive materials including water soluble macro-molecules in a continuous manner using relatively inexpensive non-toxic matrix and polymer material. As described in this specification, the method is suitable for fabricating devices of the controlled release of active material including vaccines, animal growth hormones, antibiotics and anthelmintics.

The present device also provides the basis on which further refinement or sophistication of release can be effected. For instance, by replacing the gelatin-agar matrix with biocrodible poly-ortho ester polymers prepared by the reaction between 3,9-bis (ethyiidene -2, 4, 8, 10- tetraoxaspiro [5.5] undecane) and various ratios of trans-cyclohexanedimethanol and 1,6-hexandiol (11), the production method can be readily adopted for mass production of needle injectable implants of antitumour agents such as 5-flurouracil for release in a time independent mode. Likewise, by using collagen poly (HEMA) hydrogel (10) as the incorporating matrix, needle injectable implants can be readily mass produced for a variety of hydrophilic or hydrophobic active substance with again a time independent release mode.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

REFERENCES:

1. Good, WR, Lee PI. In "Medical Applicators of Sustained Release" ed Ranger, RS and DL Wase; CRC Press. Boca Raton, FI., 1984 pp 1.

2. Baker, RW, Lonsdale, HK. In "Controlled Release of Biologically Active Agents' ed Tanquarry, AC and Lacey, RE. Advance in Experimental Medicine and Biology Series No. 47, Plenus, New York, NY, 1974, pp 15.

3. Kim, SW, Petersen, R, Feigen, J. Drug Design (1980) 10, 193.

4. Cardinal, JR, "Matrix Systems" in Medical Applications of Controlled Release" Vol. 1, Chapter 2, ed. Langer, RS and Wise DL (1984) CRC Press, Boca Raton, H. pp 41.

5. Lee, PI and Good, WR, "Overview of Controlled Release Drug Delivery" in "Controlled Release Technology, Pharmaceutical Applications', Chapter 1, ed. Lee, PT and Good, WR, ACS Symposium Series 348 (1987).

6. "Drug Release from Matrix Devices" by John R Cardinal in "Recent Advances in Drug Delivery Systems" ed. by James M Anderson and sung Wan Kim (1984) pp 229-248, Plenum Press, New York.

7. Henry Malinowski, "Regulatory review of oral - controlled drug administration: biopharmaceuticals and medical requirements", in; "Oral Controlled Drug Administration", YW Chien, ed.

8. DST Hsieh, WE Rhine and R Langer, J. Pharm. Sci., 72: 17 (1983).

9. D Brooke, US Patent # 3851648 (1974).

10. R Jeyanthi and K Pandurange Rao, "Controlled Release of Anticancer Drugs from Collagen-Poly (HEMA) Hydrogel Matrices" Journal of Controlled Release 13 (1990) 91-98.

11. YF Maa and J Heller "Controlled Release of 5-Fluorouracil from linear poly (orthoesters)", Journal of Controlled Release, 13 (1990) 11-19.

CLAIMS:

1. An implant device capable of releasing an active ingredient in an animal following administration thereto, said implant device comprising as an active ingredient at least one type of bioactive molecule, optionally admixed with one or more pharmaceutically acceptable carriers and/or excipients, substantially contained within a core matrix of a body member, said body member further comprising a membrane forming a wall around all or part of the core matrix and comprising matrial which is substantially impervious to the active ingredient and having at least one portion through which the active ingredient is capable of being released either directly or after a period of time in a continuous or pulsatile manner.

2. An implant device according to claim 1 wherein the body member is an elongate, oval, round, ball, hemispherical, capsule, rod, needle, cylindrical, sheet, film or microcapsular shape.

3. An implant device according to claim 2 wherein the body member is an elongate and/or generally cylindrical shape.

4. An implant device according to claim 1 wherein the body member is substantially elongate having at least one opening at a terminal portion thereof for release of the active ingredient directly or after a period of time.

5. An implant device according to claim 4 wherein the body member is generally cylindrical.

6. An implant device according to claim 1 or 4 wherein the portion through which the active ingredient is capable of being released is sealed or partially sealed wth a biodegradeable seal.

7. An implant device according to claim 1 wherein the wall of said body member is composed of a polymeric material.

8. An implant device according to claim 7 wherein the polymeric material is n-butyl cyanoacrylate.

9. An implant device according to claim 7 wherein the polymeric material is polylactic acid/polyglycolic acid in ratio of approximately 85:15, respectively.

10. An implant device according to claim 1 wherein said body member comprises a plurality of layers of material substantially impervious to an active ingredient interspaced between each layer.

11. An implant device according to claim 10 wherein the body member is adapted for simultaneous release of active ingredient from terminal portions of each layer.

12. An implant device according to claim 10 wherein the body member is adapted for sequential release of the active ingredient from terminal portions of each layer in turn.

13. An implant device according to claim 1 wherein the bioactive molecule in the active ingredient is a pharmaceutical substance.

14. An implant device according to claim 13 wherein the pharmaceutical substance is an antibody, cytokine, growth promotant, cancer cell inhibitory molecule or agent, immune stimulant, immune suppressant and/or hormone.

15. An implant device according to claim 1 wherein the bioactive molecule in the active ingredient is an antigen or an anti-microbial, anti-fungal or anti-viral agent.

16. An implant device according to claim 1 wherein the bioactive molecule is a nutrient, vitamin or mineral.

17. An implant device capable of releasing an active ingredient in an animal following administration thereto, said implant comprising as an active ingredient at least one type of bioactive molecule, optionally admixed with one or more pharmaceutically acceptable carriers and/or excipients, substantially contained within a core matrix of an elongate body member, said body member further comprising a membrane forming a wall around all or part of the core matrix and comprising material which is substantially impervious to the active ingredient and said elongate body member having at least one terminal portion through which the active ingredient is capable of being released either directly or after a period of time in a continuous or pulsatile manner.

18. An implant device according to claim 17 wherein the body portion is generally cylindrical.

19. An implant device according to claim 1 or 17 further comprising a central support having the active ingredient impregnated thereon or attached thereto and which central support is then coated with a material which is substantially impervious to the active ingredient to form the whole of the body member.

20. A method of manufacturing an implant device capable of releasing an active ingredient in an animal following administration thereto, said method comprising impregnating or absorbing or otherwise coating an active ingredient onto a central support, said active ingredient comprising at least one type of bioactive molecule, optionally admixed with one or more pharmaceutically acceptable carriers and/or excipients, and then coating all but at least one part of said central support and core with a material which is substantially impervious to said active ingredients such that in use, the active ingredient is capable of being released from said part either directly or after a period of time.

21. A method according to claim 20 wherein the central support is substantially elongate.

22. A method according to claim 20 or 21 wherein the said part is completely or partially sealed with a biodegradable material.

23. A method according to claim 20 wherein the central support is generally cylindrical.

24. A method according to claim 20 or 21 or 23 wherein the central support is a nylon string, polypropylene rod or surgical suture.

25. A method according to claim 24 wherein upon coating the central support with the impervious material, the terminal portions of said central support are not coated and are capable of releasing the active ingredient in a continuous manner.

26. A method according to claim 25 alternatively comprising terminal portions sealed or partially sealed with a biodegradable material.

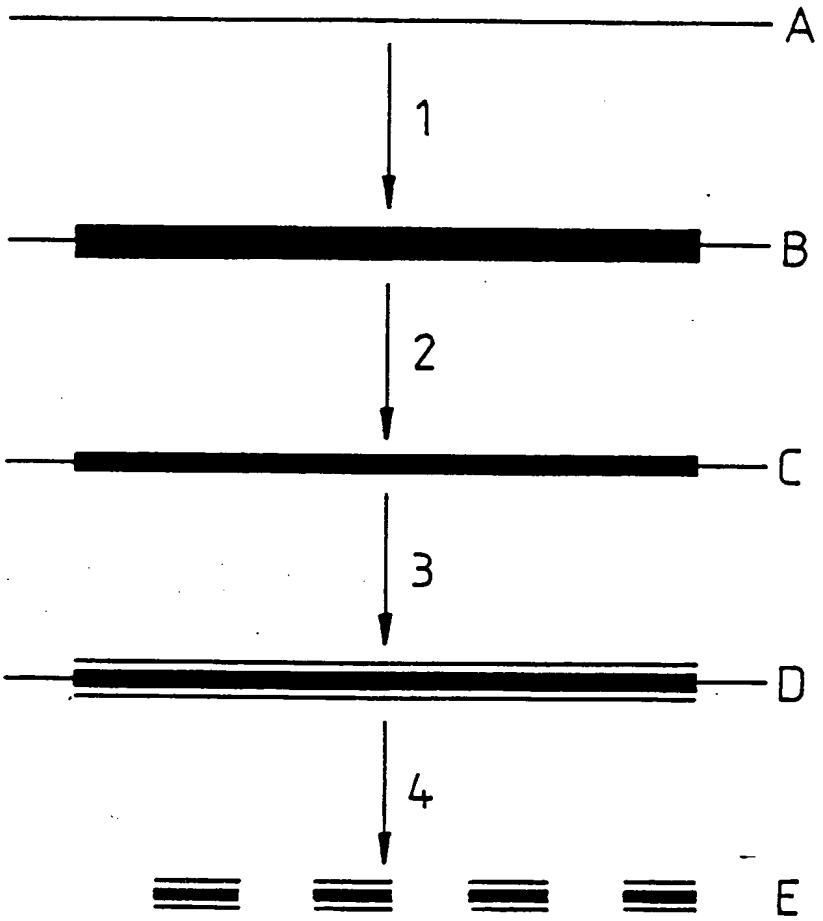


FIGURE 1

FIGURE 2

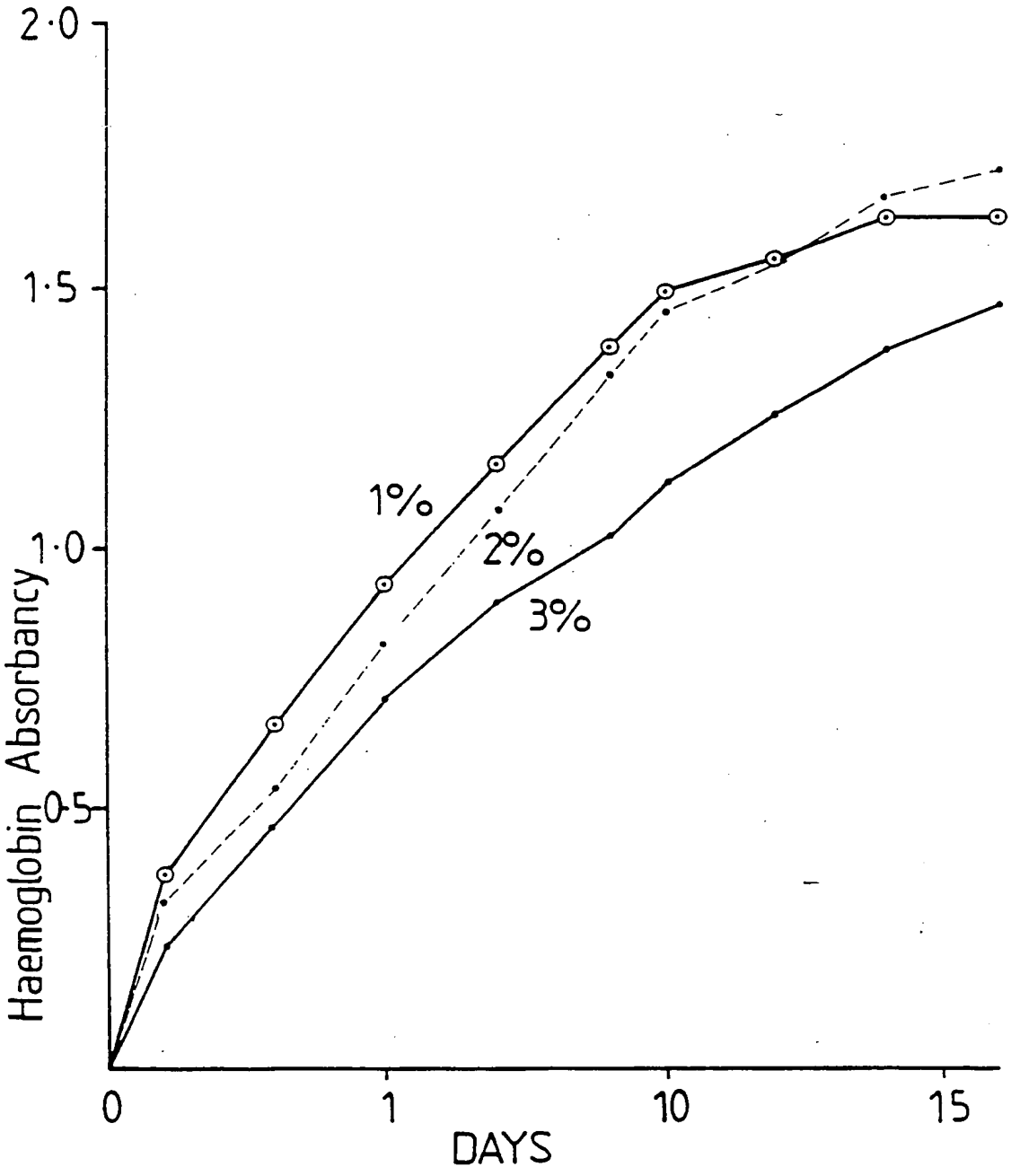
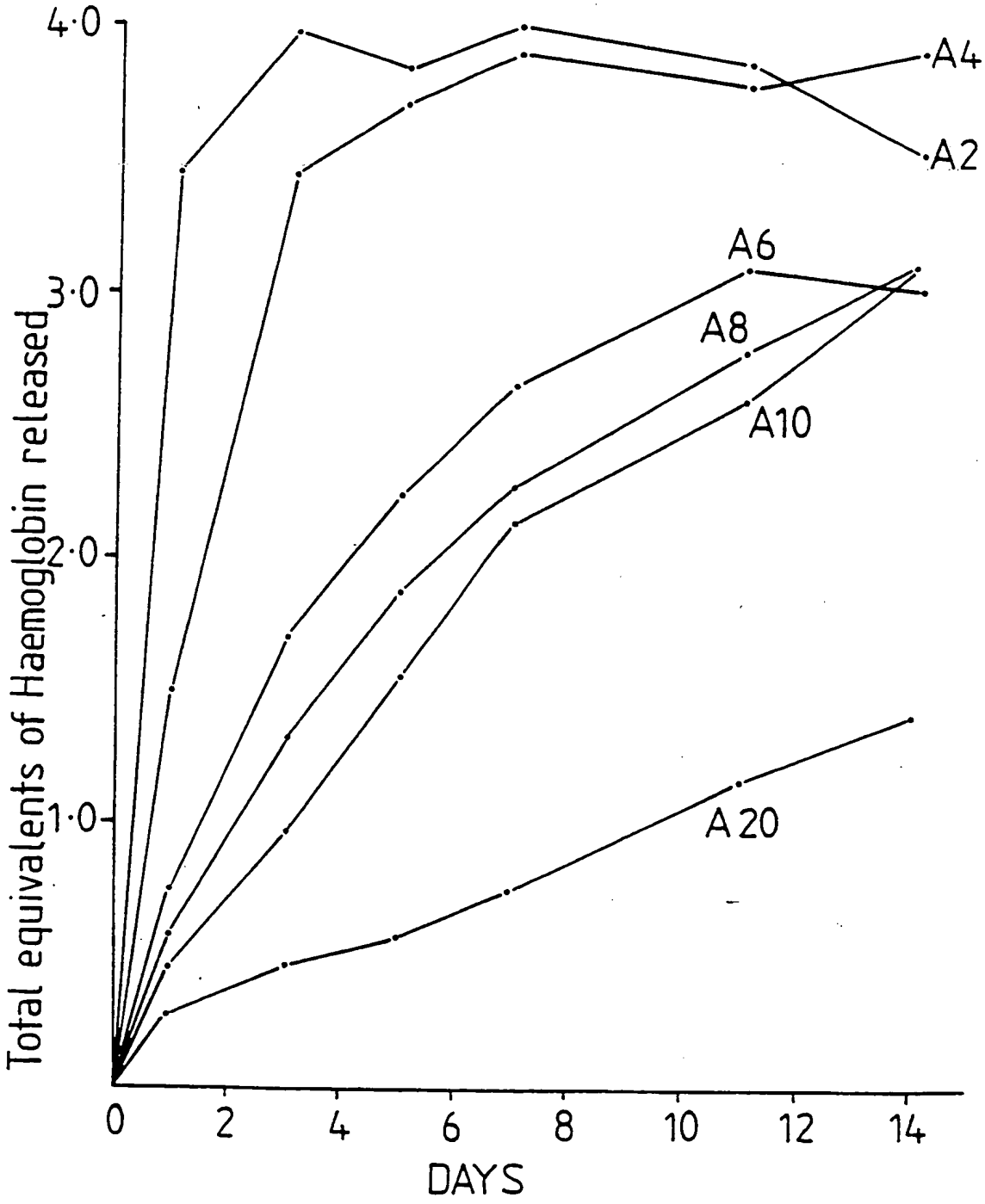


FIGURE 3



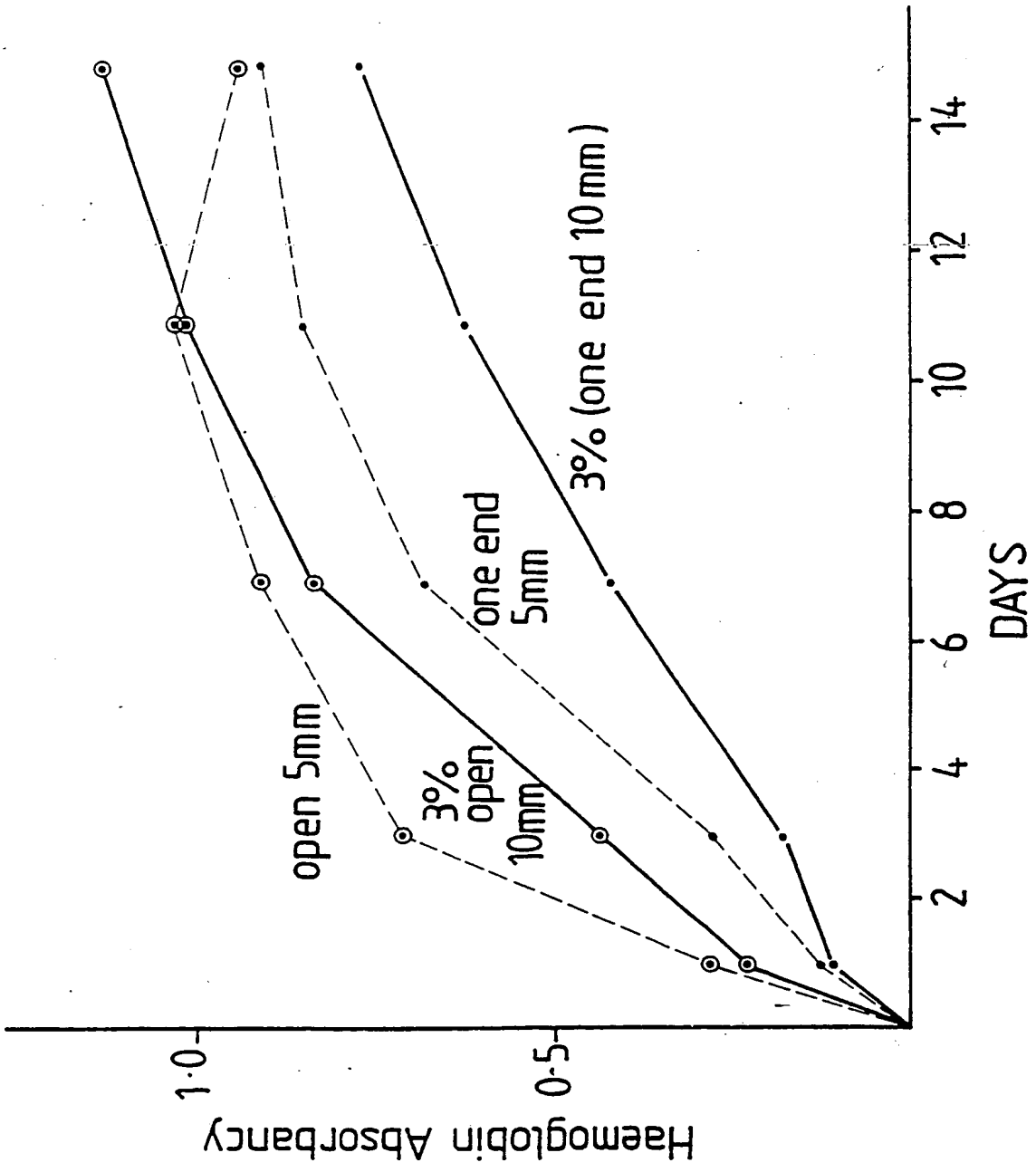


FIGURE 4

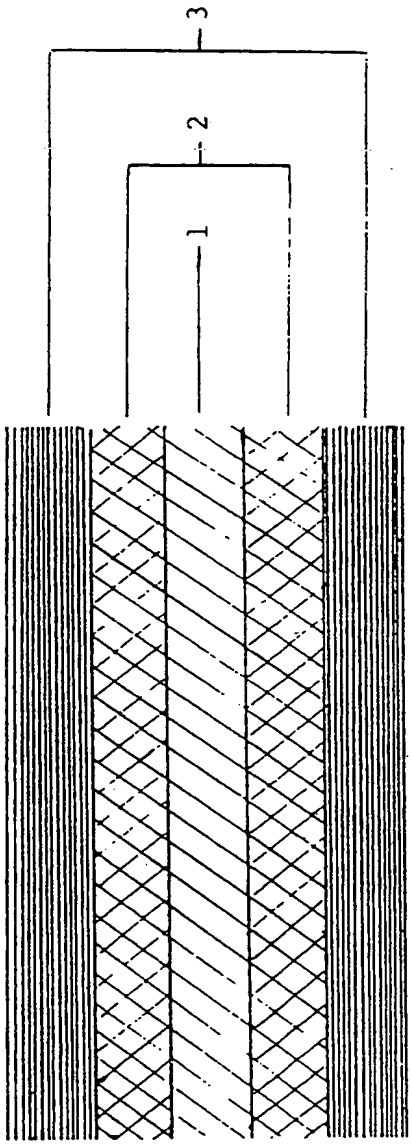


FIG 5

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl.[5] A61K 9/00 A61K 9/70 A61D 7/00 A61D 1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC A61K 9/00 A61K 9/70 A61D 7/00 A61D 1/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU : IPC as above

Electronic data base consulted during the international search (name of data base, and where practicable, search terms used)
DERWENT "implant, core matrix, membrane forming wall, rate release"
CAS ONLINE "implant, core matrix, membrane forming wall, rate release"

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	AU,B, 20449/88 (603475) (AKZO N.V.) 15 November 1990 (15.11.90) Claim 1, page 2-3	1-3, 5, 7, 13, 17 and 18
Y	Derwent Abstract Accession No. 85-242804/40, Class B04D 16, BE A, 902458 (DAMON BIOTEC INC) 16 September 1985 (16.09.85)	1-3, 5, 7 13, 17 and 18

(continued)

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
	25 MAY 1993 (25.05.93)
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. 06 2853929	Authorized officer JOHN HANSON Telephone No. (06) 2832262

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate of the relevant passages	Relevant to Claim No.
A	Chemical Abstracts, Vol. 109, No. 16, issued 17 October 1988, Columbua, Ohio, USA, Smith, Thomas J et al, "Poly (vinyl alcohol) membrane permeability characteristics of 5-fluorouracil" page 372, column 1, the abstract No. 134910z Abstract	1, 17
A	Chemical Abstracts, Vol.115, No.21, issued 25 November 1991, Columbua, Ohio, USA, Neftel, Frederic, "Implantable device for measurement of blood glucose levels", page 516, column 2, the abstract No. 227769z. Abstract	1, 17
A	Chemical Abstracts, Vol. 117, No.8, issued 24 August 1992, Columbua, Ohio, USA, Ishii Rumiko et al, "Drug delivery system of 5-flurouracil" page 430, column 1, the abstract No. 76404q. Abstract	1, 17

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
EP	303306	AU	20449/88	AU	603475	US	4957119
		US	5088505	US	900621		
BE	902458	US	3424415	AU	34505/84	GB	8428321
		GB	2159172	US	4680174	US	4044645
		US	4137812				

END OF ANNEX